Biochemistry and Pharmacology of Tryptamines and beta-Carbolines

A Minireview

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The simple derivatives of tryptamine and β-carboline (Tables I and II) are among the most widely distributed alkaloids in the plant and animal kingdoms (Allen & Holmstedt 1980; Smith 1977b). As of 1977, 19 simple derivatives of tryptamine had been identified in nature and distributed among 26 higher plant families and the Agaricales (Smith 1977b). New species are continually being added to the list (e.g., Skaltsounis, Tillequin & Koch 1983) and undoubtedly the tabulation presented by Smith (1977b) stands in need of revision. Sixty-four (64) simple β-carboline derivatives distributed among 25 higher plant families and three species of fungi had been identified as of 1980 (Allen & Holmstedt 1980). Comparison of the species cited in Smith (1977b) and those cited by Allen and Holmstedt (1980) shows that, in many instances, plants containing tryptamine derivatives also contain structurally related β-carbolines. This observation is not surprising inasmuch as β-carbolines are biosynthesized from tryptophan and/or tryptamine via condensation with one or two carbon moieties (O'Donovan, Bockley & Geary 1976; O'Donovan & Kenneally 1967) or via N-acetylation of tryptamine followed by cyclodehydration to 3,4-dihydro-β-carboline (Slaytor & McFarlane 1968). The biosynthesis of tryptamine derivatives has been reviewed by Smith (1977a).

Both tryptamine derivatives and β-carbolines have been detected as endogenous metabolites in mammals, including humans. Bufotenine and various related 5-hydroxy-indolethylamines are constituents of frog and toad venoms (Daly & Witkop 1971), being common in the genera *Hyla*, *Leptodactylus*, *Rana* and *Bufo*. A wider spectrum of bufotenine derivatives is found in the latter genus, including bufoviridine, the sulfate ester of bufotenine, dehydrobufotenine, and its sulfate ester, bufothionine. Although it is closely related to the hallucinogenic tryptamine derivatives, bufotenine itself is not hallucinogenic (Kantor, Dudlettes & Shulgin 1980), acting as a pressor rather than a hallucinogen in humans. The skin of *Bufo alvarius* contains 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) at the rather staggering concentration of 50-160 mg/g of skin (Daly & Witkop 1971). This is the only *Bufo* species known to contain a hallucinogenic tryptamine. Methyl transferases that catalyze the synthesis of tryptamines, including dimethyltryptamine (DMT), 5-MeO-DMT and bufotenine, have been characterized in human lung, brain, blood, cerebrospinal fluid, liver and heart, and also in rabbit lung and toad, mouse, steer, guinea pig and baboon brains as well as in other tissues in these species (Barker, Monti & Christian 1981). The in vivo formation of DMT from labeled precursors has been demonstrated in rabbit lung and in rat brain (Barker, Monti & Christian 1981). These investigators have also summarized the state of knowledge of DMT biosynthesis in mammals as of 1981. Endogenous β-carboline derivatives have also been detected in human and rat tissues. Both tetrahydro-β-carbolines and the fully aromatic derivatives have been detected (Melchior & Collins 1982). An aromatic β-carboline has been isolated from aging human lens protein (Dillon, Spector & Nakanishi 1976), which

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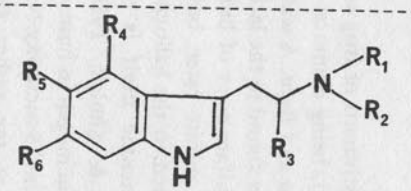
TABLE I

SOME NATURALLY-OCCURRING TRYPTAMINE DERIVATIVES*



Name of Compound	Abbreviation	Substitution Pattern: R_1	R_2	R_3	R_4	R_5	R_6
tryptophan	-	H	H	COOH	H	H	H
5-hydroxy-tryptophan	-	H	H	COOH	H	OH	H
tryptamine	TA	H	H	H	H	H	H
5-hydroxy-tryptamine	5HT	H	H	H	H	OH	H
N-methyl-tryptamine	NMT	H	CH_3	H	H	H	H
5-methoxy-tryptamine	5-MeO-T	H	H	H	H	OCH_3	H
6-methoxy-tryptamine	6-MeO-T	H	H	H	H	H	OCH_3
5-methoxy-N-methyl-tryptamine	5-MeO-NMT	H	CH_3	H	H	OCH_3	H
5-methoxy-N-acetyl-tryptamine (melatonin)	-	H	$O{=}CCH_3$	H	H	OCH_3	H
N,N-dimethyl tryptamine	DMT	CH_3	CH_3	H	H	H	H
5-hydroxy-N,N-dimethyl-tryptamine (bufotenine)	5HO-DMT	CH_3	CH_3	H	H	OH	H
5-methoxy-N,N-dimethyl-tryptamine	5MeO-DMT	CH_3	CH_3	H	H	OCH_3	H
4-hydroxy-N,N-dimethyl-tryptamine (psilocin)	4HO-DMT	CH_3	CH_3	H	OH	H	H
4-phosphoryl-N,N-dimethyl-tryptamine (psilocybin)	-	CH_3	CH_3	H	OPO_3H	H	H
4-phosphoryl-N-methyl-tryptamine (baeocystine)	-	H	CH_3	H	OPO_3H	H	H
4-phosphoryl-tryptamine (norbaeocystine)	-	H	H	H	OPO_3H	H	H
N-methyl-tryptophan-methyl ester (abrine methyl ester)	-	H	CH_3	$COOCH_3$	H	H	H
N,N-dimethyl-tryptophan	-	CH_3	CH_3	COOH	H	H	H

*See Table III for structures of some psychoactive synthetic tryptamine derivatives.

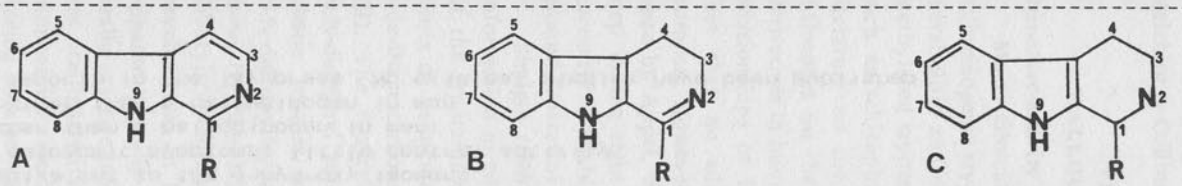
TABLE II

SOME NATURALLY-OCCURRING β-CARBOLINE DERIVATIVES

*See Table III for structures of some psychoactive synthetic tryptamine derivatives.

TABLE II

SOME NATURALLY-OCCURRING β-CARBOLINE DERIVATIVES



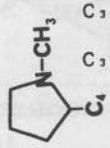
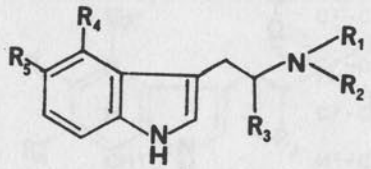
Trivial Name	Ring Type	R=	Additional Substitutents & Their Location	Abbreviation
norharman	A	H	-	-
norharmalan	B	H	-	-
tetrahydro-norharman	C	H	-	-
harman	A	CH_3	-	-
harmalan	B	CH_3	-	-
tetrahydro-harman	C	CH_3	-	-
harmine	A	CH_3	C_7-OCH_3	-
harmaline	B	CH_3	C_7-OCH_3	-
tetrahydro-harmine	C	CH_3	C_7-OCH_3	-
harmic amide	A	$CONH_2$	C_7-OCH_3	-
acetyl norharmine	A	$C{=}OCH_3$	C_7-OCH_3	-
harmine N-oxide	A	CH_3	C_7-OCH_3, N_2-->O	-
ketotetrahydro-norharmine	C	=O	C_7-OCH_3	-
harmic acid methyl ester	A	$COOCH_3$	C_7-OCH_3	-
harmalinic acid	B	COOH	C_7-OCH_3	-
harmol	A	CH_3	C_7-OH	-
harmalol	B	CH_3	C_7-OH	-
6-methoxy-harman	A	CH_3	C_6-OCH_3	-
6-methoxy-harmalan	B	CH_3	C_6-OCH_3	-
6-methoxy-tetrahydro-harman	C	CH_3	C_6-OCH_3	-
6-methoxy-2-methyl-tetrahydro-β-carboline	C	H	N_2-CH_3, C_6-OCH_3	6-MeO-MTHβC
6-methoxy-1,2-dimethyl-tetrahydro-β-carboline	C	CH_3	N_2-CH_3, C_6-OCH_3	6-MeO-DMTHβC
2-methyl-tetrahydro-β-carboline	C	H	N_2-CH_3	MTHβC
1,2-dimethyl-tetrahydro-β-carboline	C	CH_3	N_2-CH_3	DMTHβC
β-carboline-3-carboxylate	A	H	C_3-COOH	βCC
β-carboline-3-carboxylate ethyl ester	A	H	C_3-$COOCH_3$	βCCEE
tetrahydroharman-3-carboxylate	C	CH_3	C_3-COOH	-
brevicoline	A	CH_3		-

TABLE III

ORALLY AND PARENTERALLY ACTIVE PSYCHOTROPIC TRYPTAMINE DERIVATIVES*



Name of Compound	Substitution Pattern R1	R2	R3	R4	R5	Dosage (mg)	Route: Oral/Parenteral
tryptamine	H	H	H	H	H	100†	par/oral?
DMT	CH_3	CH_3	H	H	H	60	par
DET	C_2H_5	C_2H_5	H	H	H	60	par/oral
DPT	n-prop	n-prop	H	H	H	60	par/oral
DAT	C_3H_5	C_3H_5	H	H	H	60	par/oral
DIPT	i-prop	i-prop	H	H	H	30	oral
5MeO-DIPT	i-prop	i-prop	H	H	OCH_3	12	oral
5MeO-DMT	CH_3	CH_3	H	H	OCH_3	6	par
psilocin	CH_3	CH_3	H	OH	H	12‡	oral
CZ-74	C_2H_5	C_2H_5	H	OH	H	15‡	oral
serotonin	H	H	H	H	OH	100#	oral
bufotenine	CH_3	CH_3	H	H	OH	16þ	par
IT-290	H	H	CH_3	H	H	30	oral
4-hydroxy-α-methyl-tryptamine	H	H	CH_3	OH	H	20#	oral
MP-809	H	H	CH_3	H	CH_3	60ξ	oral
5-fluoro-α-methyl-tryptamine	H	H	CH_3	H	F	25ϕ	oral
5-methoxy-α-methyl-tryptamine	H	H	CH_3	H	OCH_3	3	oral
4-hydroxy-diisopropyl-tryptamine	i-prop	i-prop	H	OH	H	12ϕ	oral
4-hydroxy-N-isopropyl,N-methyl-tryptamine	i-prop	CH_3	H	OH	H	6ϕ	oral
N-t-butyl-tryptamine	H	t-butyl	H	H	H	?ϕ	oral
3-[2-(2,5-dimethylpyrrolyl)ethyl]-indole			H	H	H	?	?

* Data compiled from Kantor, et al.,1980; Shulgin, 1976,1982; Shulgin & Carter, 1980.
† Autonomic symptoms; little central activity.
‡ The phosphate esters are psilocybin and CEY-19, respectively; both are stoichiometrically equivalent to the 4-hydroxy isomers.
# Cardiovascular and autonomic symptoms; little central activity.
þ A pressor amine rather than a hallucinogen in man.
ξ An antidepressant rather than a hallucinogen in man.
ϕ Based on anonymous reports in the lay press. No clinical studies have been published.

is interesting in light of the recently discovered photocytotoxicity of aromatic β-carbolines (McKenna & Towers 1981). Endogenous β-carboline derivatives and tetrahydroisoquinolines have been detected in human urine following ethanol loading (Bloom et al. 1982; Melchior & Collins 1982).

PHARMACOLOGY OF HALLUCINOGENIC TRYPTAMINES

Structure-activity Relationships

Most clinical and pharmacological studies with hallucinogenic tryptamines have focused on their in vitro metabolism and/or the possible endogenous synthesis of methylated tryptamine derivatives in pathological states such as schizophrenia. There is a paucity of scientific literature on the systematic investigation of structural influences on the hallucinogenic activity of tryptamine derivatives in humans. Investigations of structure-activity relationships of hallucinogens are complicated by the fact that no adequate animal model exists for this purpose. However, the drug discrimination test developed by Appel, White and Holohean (1982) represents a step in the right direction. As a result, much of the currently available information is derived from underground sources of dubious credibility.

Shulgin (1982, 1976) has summarized the available information in two recent reviews. The substitution sites of the tryptamine nucleus that are important determinants of hallucinogenic activity are the indole ring, the side-chain carbons or the side-chain nitrogen (see Table III). The N-alkyl homologues of DMT in which the N,N-dimethyl substituents are replaced with more aliphatic moities include N,N-diethyltryptamine (DET), N,N-dipropyltryptamine (DPT), N,N-diisopropyltryptamine (DIPT), N,N-diallyltryptamine (DAT) and N,N-dibutyltryptamine (DBT). All of these homologues are psychoactive in humans except for DBT, and all are apparently orally active except for DMT itself, which is orally inactive in doses exceeding 1,000 mg. Presumably, the oral inactivity of DMT is due to its deamination by monoamine oxidase (MAO), while those derivatives having bulkier N-alkyl substituents are orally active due to steric hindrance of the enzyme. Potency of all of the N,N-dialkyl derivatives mentioned above is considerably enhanced by hydroxyl substitution at the indole 4-position. This substitution on DMT also confers oral activity on the parent compound, creating psilocin (4-hydroxy-DMT). The mechanism underlying the oral activity of psilocin is unelucidated, but is probably due to the formation of an intramolecular ionic bond between the anionic ring hydroxyl and the charged side-chain nitrogen. This configuration could form a pseudo C ring and thus protect the side chain from deamination (Kantor, Dudlettes & Shulgin 1980). Interestingly, the 5-hydroxyl isomer of psilocin, bufotenine, is inactive as a hallucinogen and acts primarily on the peripheral autonomic system causing severe cardiovascular stimulation, salivation, hypertension, lachrymation and hyperventilation, but no central effects (Shulgin 1982). Apparently the 5-hydroxy substitution does not permit the formation of the intramolecular zwitterionic bond, and the anionic character of the oxygen substituent interferes with the uptake of the compound into the central nervous system (CNS).

The 5-O-methyl analogue of bufotenine (5-MeO-DMT) is parenterally active as a hallucinogen in humans, but is not orally active. 5-MeO-DMT exhibits similar psychological and somatic symptoms in humans as DMT, but is approximately an order of magnitude more potent on a milligram basis (see Table III). Both 5-MeO-DMT and bufotenine are closely related structurally to the CNS transmitter serotonin (5-hydroxytryptamine). The N,N-diisopropyl analogues of DMT and 5-MeO-DMT are both orally active as hallucinogens in humans (Shulgin & Carter 1980). Little is known of the hallucinogenic activity of the N-monosubstituted, N-dealkyl or N-cycloalkyl tryptamines. The mono-tert-butyl derivative is reputed to be orally active (Shulgin 1982).

In addition to indole ring substituents and aliphatic N-alkyl substituents, the side-chain α-carbon represents a third substitution site affecting hallucinogenic activity. Methyl substitution of the α-carbon confers oral hallucinogenic activity on the compounds α-methyltryptamine and 5-MeO-α-methyltryptamine (Shulgin 1982; Kantor, Dudlettes & Shulgin 1980). The mechanism of oral activity in the case of these analogues is undoubtedly related to steric hindrance of enzymatic deamination by the α-substituent. α-Methyltryptamine and α-ethyltryptamine have been shown to act as competitive inhibitors of MAO (Greig, Walk & Gibbon 1959). No information is available on the activity of α-substituted N,N-dialkyltryptamines.

Metabolism of Hallucinogenic Tryptamines

The synthetic and degradative metabolism of DMT in mammals has been recently reviewed (Barker, Monti & Christian 1981). Indole N- and O-methyl transferases that catalyze the synthesis of DMT, 5-MeO-DMT and bufotenine have been characterized in human lung, brain, blood and cerebrospinal fluid (Rosengarten & Friedhoff 1976). Tryptamine, 5-hydroxytryptamine (5-HT) and N-methyltryptamine (NMT) have been identified as substrates for indole-N-methyltransferases (INMTs), but there is considerable variation in substrate

specificity in different organisms and tissues. Two INMTs have been characterized in the Australian grass *Phalaris tuberosa* that have different affinities for the primary amine (tryptamine) and the secondary amine (NMT), indicating that both are required in the biosynthesis of the tertiary amine (Mack & Slaytor 1979). The presence of two or more types of INMTs in mammals has not been proven, but would explain the varying substrate affinities in different tissues of the same species. S-adenosylmethionine (SAM) functions as the methyl donor in the transmethylation reaction. However, both SAM and 5-methyltetrahydrofolic acid (MTHF) have been found to participate in the synthesis of 2-methyl-tetrahydro-β-carboline (MTHβC) and tetrahydro-β-carboline (THβC) when incubated in vitro with NMT and tryptamine, respectively (Barker, Monti & Christian 1980). The THβC formation probably occurs via the enzymatic formation of formaldehyde (HCHO) from the methyl donors followed by nonenzymatic condensation with the indole substrates via a Pictet-Spengler reaction. Both DMT and adenosine-SH (SAH), the demethyl derivative of SAM, are potent inhibitors of the INMT activity (Barker, Monti & Christian 1980). Possible mechanisms involved in the regulation of the INMT activity have been reviewed by Barker, Monti and Christian (1981).

These investigators (1980) also carried out a quantitative study of the degradative metabolism of DMT in rat whole brain homogenates using deuterated DMT and found indole-3-acetic acid (IAA), NMT, MTHβC and DMT-N-oxide as metabolites. IAA was the major metabolite when DMT was incubated at 6×10^{-8} M, but at 2×10^{-5} M, DMT-NO was the major metabolite. Incubation of 6×10^{-8} M DMT in homogenates obtained from rats pretreated with the MAO inhibitor (MAOI) iproniazid resulted in the inhibition of IAA formation by 83 percent, while NMT and DMT-NO formation was inhibited by 90 percent and no MTHβC was formed.

Based on these observations, Barker, Monti and Christian (1980) speculated that a high proportion of IAA probably arose as a secondary metabolite resulting from the oxidative deamination of NMT. DMT itself is a poor substrate for MAO (Barlow 1961: Udenfriend et al. 1958). The relative rate of oxidation of NMT is some nine times faster than DMT and 280 times faster than DMT-NO. The THβCs detected as trace metabolites may be formed from the nonenzymatic condensation of tryptamine and/or NMT with the HCHO formed as an intermediate in the N-demethylation of DMT. Barker, Monti and Christian (1980) have made the interesting observation that direct C-hydroxylation of tertiary amines and tertiary amine N-oxide rearrangement results in the formation of identical intermediates (carbinolamines, iminium ions), which can undergo intramolecular cyclization to THβCs.

Earlier studies of DMT metabolism in rat liver microsomes obtained from animals pretreated with iproniazid detected 6-hydroxy-DMT and 6-hydroxy-DMT-NO in addition to tryptamine, NMT and DMT-NO, giving rise to speculation that 6-hydroxylation might be an important metabolic pathway for DMT (Szara & Axelrod 1959). More recent studies have shown that while 6-hydroxylation is characteristic of DMT metabolism in peripheral tissues, it apparently does not occur in brain (Barker, Monti & Christian 1980).

Other investigators have focused on the metabolism of 4-hydroxy-DMT or psilocin (Kalberer, Kreis & Rutschmann 1962; Horita & Weber 1961). These studies indicated that oxidative deamination of the side chain may be a relatively minor route of degradation for this compound. A metabolic study of the fate of ^{14}C-psilocin in the rat (Kalberer, Kreis & Rutschmann 1962) indicated that unchanged psilocin and 4-hydroxy-IAA accounted for only 40 percent of total urinary metabolites, the remainder being present as extremely hydrophilic metabolites that could not be positively identified as glucuronides. Horita and Weber (1961) studied the incubation of psilocybin in rat kidney homogenates. They found that psilocybin was readily dephosphorylated to psilocin by alkaline phosphotase. Psilocin was then rapidly metabolized to a blue-colored product, which they speculated was the o-quinone of psilocin. The formation of the blue product was unaffected by the presence of MAOIs, but could be inhibited by cyanide (KCN). Subsequently, psilocin and other hydroxyindoles, including serotonin and bufotenine, were shown to be oxidized to colored products in the presence of mammalian cytochrome oxidase (Weber & Horita 1963). The significance of these metabolic investigations of DMT, psilocin and related tryptamines lies in the recognition that oxidative deamination by MAO is not necessarily the only, or even the major, pathway available for the degradative metabolism of these compounds.

Hallucinogenic Tryptamines and MAO Inhibition

The activity of some tryptamine derivatives as MAOIs has been investigated (Ho et al. 1970; Lessin, Long & Parkes 1967; Barlow 1961). Unlike the β-carbolines, however, extensive studies of the structure-activity relationships of tryptamines with respect to MAOI activity have not been carried out. Lessin, Long & Parkes (1967) examined the structure-activity relationships of a series of substituted tryptamines and β-carbolines on

activity as MAOIs and inhibitors of 5-HT uptake. Among the tryptamines the most potent analogue was 6-MeO-α,α-dimethyltryptamine, which had 1.5 percent of the inhibitory potency of harmaline. The activity of N,N-DMT, 2-methyl-DMT and 5-benzyloxy-DMT as MAOIs in the guinea pig liver was investigated at various inhibitor and substrate concentrations (Barlow 1961). In all cases DMT had significantly more activity than the other derivatives. The activity of DMT as a MAOI was also influenced by the substrate: greatest inhibition was observed with 5-HT as substrate, intermediate inhibition with tyramine as substrate, while the lowest activity was found with tryptamine as substrate. These results are consistent with the postulate that DMT may be a specific inhibitor of one form of MAO: MAO-A. Ho and colleagues (1970) investigated the MAOI activity of a series of 5-substituted gramines, α-methyltryptamines and DMTs using tryptamine as substrate. The order of MAOI activity of the tryptamine derivatives was DMT > 5-methyl-DMT > 5-MeO-DMT > 5-hydroxyl-DMT. The DMT derivatives were generally more potent than the gramine derivatives except for 5-bromo-gramine, which gave comparable inhibition at 72 percent of the concentration of DMT.

The potentiation of the behavioral and pharmacological effects of tryptamine derivatives by MAOIs has been investigated, although the specific question of the oral potentiation of DMT and other parenterally-active derivatives has apparently not been investigated. The effect of DMT in human volunteers was assessed before and three days after treatment with the MAOI iproniazid (Sai-Halasz 1963). Patients receiving DMT at a reduced dose following the iproniazid treatment experienced none of the visual illusions or disturbances of time and space perception that typify the symptoms of the drug. They reported only a feeling of "strangeness." Patients receiving a dose equivalent to that prior to iproniazid had a two-phase response. The first stage was similar to the usual DMT effects, but less pronounced: illusions and hallucinations were present but less colorful and only manifested themselves with the eyes closed. The second phase was characterized by a persistent feeling of "strangeness" to which the patients often reacted negatively or indifferently. Based on these trials, Sai-Halasz (1963) speculated that the reduced effects may have been due to the higher 5-HT concentration in the brain due to MAO inhibition, thus mitigating the 5-HT blocking effects of DMT. This speculation was also supported by the observation that prior administration of 1-methyl-d-lysergic acid butanolamide, a powerful serotonin antagonist, greatly exacerbated the psychotomimetic effects of DMT (Sai-Halasz 1962).

Moore, Demetriou and Domino (1975) studied the effects of iproniazid, chlorpromazine and methiothepin on DMT-induced changes in body temperature, pupillary dilatation, blood pressure and EEG in rabbits. Chlorpromazine attenuated or blocked the effects of DMT on these parameters, but iproniazid prolonged the elevated rectal temperatures and mydriasis induced by DMT. Arterial blood pressure and EEG were not markedly altered by pretreatment with iproniazid.

Wang-Lu and Domino (1976) investigated the effect of the MAOIs iproniazid and tranylcypromine on DMT halflife in rat liver and brain, and found a greatly increased halflife in both tissues after treatment. Tranylcypromine prolonged DMT halflife more than iproniazid. Interestingly, treatment with a larger dose of DMT in the absence of MAOI prolonged the halflife in brain but not in liver. The authors speculated that this may be due to the fact that DMT itself is a weak MAOI and that its clearance from brain is mainly dependent on MAO. Liver may have other enzymes capable of metabolizing DMT even though MAO is inhibited. Halflife in brain and liver was similar in the presence of MAOI, indicating that similar enzymes participate in the metabolism of DMT following MAO inhibition.

Shah and Hedden (1977) studied behavioral effects and metabolism of DMT in mice pretreated with SKF-525A, iproniazid, and chlorpromazine and found that iproniazid prolonged the behavioral effects of DMT and also significantly elevated DMT levels in plasma, brain and liver with respect to controls. SKF-525A, an inhibitor of a wide variety of hepatic microsomal enzymes, did not prolong the behavioral effects of DMT or result in increased tissue or plasma levels, thus providing further evidence that MAO is the primary enzyme involved in the metabolism of DMT in vivo. It also indicated that the central effects of DMT are due to the parent compound rather than the 6-hydroxy metabolite detected in some studies (e.g., Szara & Axelrod 1959). 6-Hydroxy derivatives of DMT and related compounds are inactive as hallucinogens (Shulgin 1976).

Although the available literature indicates that MAOIs do have significant influences on both the metabolism and behavioral effects of DMT, apparently the specific interactions of DMT with β-carbolines have not been investigated. This apparent oversight is especially remarkable in view of the close structural relationships of tryptamine derivatives and β-carbolines (see Tables I and II), the probable metabolic interconversion of DMT, other tryptamines and β-carbolines (Barker, Monti & Christian 1980; Hsu & Mandell 1975), the involvement of both classes of compounds in important neuroregulatory functions such as MAO activity and

amine uptake (Bloom et al. 1982; Melchior & Collins 1982; Lessin, Long & Parkes 1967) and the probable role of tryptamine and β-carboline combinations in the mechanism of oral activity of the hallucinogen *ayahuasca* (McKenna, Towers & Abbott 1984). The available evidence strongly suggests that tryptamines and β-carbolines are closely related, not only structurally but also pharmacologically, yet very little is known about their interactions in mammalian systems.

BIOCHEMISTRY AND PHARMACOLOGY OF β-CARBOLINE DERIVATIVES

β-Carbolines have been known to science since the isolation of harmaline from *Peganum harmala* by Goebel in 1847, followed a few years later by the isolation of harmine from the same species by J. Fritsche (Holmstedt 1982). The structure elucidation of both compounds was accomplished by Manske in 1927 and their total synthesis was published by Spath and Lederer in 1930. In spite of their long history, many aspects of the biochemistry and pharmacology of β-carboline derivatives remain poorly understood. Since the discovery in 1958 that harmaline and related derivatives are competitive, reversible inhibitors of MAO (Udenfriend et al. 1958), there has been a resurgence of interest in β-carbolines. The following section focuses primarily on the psychopharmacology of β-carbolines. Other aspects of their pharmacology have been discussed by Ho (1977) and will only be mentioned here.

Psychopharmacology of β-Carboline Derivatives

β-Carbolines as MAOIs. The activity of β-carbolines as competitive, reversible inhibitors of MAO was first demonstrated by Udenfriend and colleagues (1958). Subsequently, structure-activity relationships were investigated by Buckholtz and Boggan (1977, 1976), Ho and colleagues (1968), and McIsaac and Estevez (1966). Direct comparison of the results of these studies are complicated by the use of different animals and tissues as the source of MAO as well as by the use of different substrates. Other investigations (Donnelly & Murphy 1977; Donnelly, Richelson & Murphy 1976; Houslay & Tipton 1974; Fuller, Warren & Molloy 1970) have produced evidence that at least two species of MAO exist. These forms of MAO, designated MAO-A and MAO-B, have different substrate specificities, are differentially sensitive to various MAO inhibitors and have different kinetic properties.

Fuller, Warren and Molloy (1970) demonstrated that harmaline (and presumably other β-carbolines) is a selective inhibitor of MAO-A. Some structure-activity relationship studies of β-carboline MAOI activity have used tyramine as substrate (McIsaac & Estevez 1966), others have used tryptamine (Buckholtz & Boggan 1977, 1976; Ho et al. 1968) and still others have used tryptamine, 5-HT and β-phenylethylamine as substrate (Buckholtz & Boggan 1977). 5-Hydroxytryptamine is a specific substrate of MAO-A while tryptamine and tyramine are substrates of both MAO-A and MAO-B. β-Phenylethylamine is probably metabolized mainly by MAO-B in vivo (Neff & Yang 1974). In view of the different substrates and enzyme species used in different studies it is not surprising that there are considerable differences in the I_{50} values and other structure-activity parameters. McIsaac and Estevez (1966), using tyramine as substrate, found that fully aromatic β-carbolines were most active as MAOI while tetrahydro-β-carbolines had the least activity. Dihydro- derivatives were intermediate in potency; a result that agrees with other studies. Little difference in potency was found between 6- or 7-methoxylated or unsubstituted β-carbolines, but hydroxyl substitution reduced the activity. Buckholtz and Boggan (1977) using tryptamine as substrate reported results in general agreement with those of McIsaac and Estevez except that 7-methoxy-β-carbolines were more potent than 6-methoxy- or unsubstituted derivatives. Methyl substitution at C_1 decreased activity for liver MAO but increased it for brain MAO. Other differences in potency between liver and brain MAO were also noted for various derivatives. In general, most β-carbolines gave lower I_{50} values with 5-HT as substrate than with tryptamine as substrate. Ho and colleagues (1968) studied the influence of various substituents on C_1, N_2 and N_9 of the β-carboline nucleus on MAOI activity. Methyl, ethyl or carboxyl substitution of C_1 resulted in a progressive decrease in activity, as the carboxyl substituted compounds are some 18 times less active than the unsubstituted derivatives. Ethyl or N-propyl substitution of N_2 did not significantly reduce activity, although N_2-acetyl substitution essentially abolished the activity. Methyl substitution of the indolic nitrogen (N_9) significantly enhanced activity of the tetrahydro-β-carbolines but only slightly enhanced the aromatic derivatives. Buckholtz and Boggan (1976) studied tetrahydro-β-carbolines in mouse brain and liver, and found that they were more potent inhibitors in brain than in liver. 6-Methoxy-tetrahydro-β-carboline (6-MeO-THβC) was without inhibitory activity in liver but had about the same activity in brain as THβC.

β-Carbolines as hallucinogens. The little that is known about the hallucinogenic activity of β-carbolines stems primarily from the studies of Naranjo (1967) and Pennes and Hoch (1957). No systematic human studies of the hallucinogenic activity of β-carboline derivatives

have been conducted in over 25 years and many of the results reported by Naranjo were obtained from a single human trial. What does seem clear, however, is that the hallucinogenic action of β-carbolines only manifests itself at threshold dosage levels that are several orders of magnitude greater than the doses required to manifest their activity as MAOIs or as competitive inhibitors of 5-HT and epinephrine uptake (e.g., Buckholtz & Boggan 1977, 1976). It is unlikely, therefore, that these activities can be invoked as the mechanism responsible for the hallucinogenic action of some β-carbolines. Pennes and Hoch (1957) reported that harmine was orally inactive at doses in excess of one gram, but observed threshold hallucinogenic effects at intravenous doses between 200-250 mg. Slotkin, DiStefano and Yu (1970) observed comparable effects at 50 mg intravenously. Naranjo (1967) reported that harmaline was orally active at 4.0 mg/kg, while tetrahydroharmine was apparently less active. However, the equation 300 mg tetrahydroharmine is equal to 100 mg harmaline resulted from a single trial. Naranjo (1969) reported that the 6- substituted analogue of harmaline (6-MeO-harmalan) gave threshold oral activity at 1.5 mg/kg. Comparable levels of 6-MeO-tetrahydroharmine gave "milder effects." 6-MeO-harman, the analogue of harmine, has apparently not been investigated.

Endogenous synthesis of β-carbolines in mammals. The hypothesis that endogenously synthesized hallucinogens might play a role in the etiology of schizophrenia or other mental disorders has fallen in and out of favor among researchers ever since Osmond and Smythies (1952) first proposed the idea. The issue has still not been resolved, even though unequivocal evidence has been obtained that hallucinogens can arise in mammalian systems under certain conditions. McIsaac (1961a) was the first to suggest that an endogenous β-carboline, formed from the cyclodehydration of the pineal hormone melatonin (5-methoxy-N-acetyltryptamine), could be an etiological factor in mental illness. Subsequently, McIsaac (1961b) demonstrated that 1-methyl-6-MeO-THβC could be formed from 6-MeO-tryptamine and acetaldehyde under mild physiological conditions in vitro and also in vivo in rats pretreated with iproniazid and disulfiram (Antabuse®). The hypothesis appeared to be confirmed when Farrel and McIsaac (1961) claimed to have isolated a pineal hormone, adrenoglomerulotropin, which was identical to 1-methyl-6-MeO-THβC. This initial tentative identification could not be confirmed and eventually the claim was withdrawn (Farrell, McIsaac & Taylor 1964). Although McIsaac's original hypothesis that the pineal gland is a likely site of endogenous β-carboline formation has only been confirmed for birds (Kari 1981), the evidence that β-carbolines are synthesized in a variety of tissues is now overwhelming. β-Carbolines have been unequivocally identified in human plasma and platelets, and in the rat whole brain, forebrain, arcuate nucleus and adrenal gland.

Most of the endogenous β-carbolines so far characterized are 6-methoxy-, 6-hydroxy- or unsubstituted tetrahydro-β-carbolines. However, the fully aromatic derivative harman has been found in the rat arcuate nucleus (Melchior & Collins 1982). It has been shown (Rommelspacher, Caper & Strauss 1976; Hsu & Mandell 1975) that in some instances endogenous β-carbolines are formed as result of condensation of indolamines with HCHO released nonenzymatically from 5-methyl-tetrahydrofolic acid (MTHF). Recent interest has centered on the possible involvement of endogenous β-carbolines, tetrahydroisoquinolines and other amine-aldehyde condensation products in the etiology of alcoholism (Rahwan 1975; Davis & Walsh 1970). 2-Methyl-THβC and harman were identified in human urine after ethanol loading (Rommelspacher, Strauss & Lindemann 1980). Presumably these constituents are formed via the condensation of biogenic amines such as serotonin or dopamine with acetaldehyde, the primary metabolite of ethanol. See Bloom and coeditors (1982) and Melchior and Collins (1982) for recent comprehensive reviews of the biochemistry, pharmacology and pathology of endogenous mammalian alkaloids.

Other Neurological and Biological Activities of β-Carbolines

β-Carbolines exhibit a wide spectrum of neurophysiological and biological activities in addition to those discussed above. A number of β-carbolines have been shown to inhibit the uptake of 5-HT, dopamine, norepinephrine and epinephrine into synaptosomal suspensions (Ho 1977; Buckholtz & Boggan 1976). Other β-carboline derivatives are inhibitors of membrane adenosinetriphosphatases (ATPases) in human erythrocytes, rat brain and squid retinal axon (Ho 1977; Canessa, Jaimovich & de la Fuente 1973). Interference with synthesis of biogenic amines by some β-carbolines has also been reported (Ho 1977). β-Carboline-3-carboxylate ethyl ester (βCCEE) and other β-carboline derivatives have been implicated (Lapin 1983; Mennini, Cotecchia & Garattini 1982) as possible endogenous ligands for the benzodiazepine receptors, although other compounds, including purines and kynuramines, have also been proposed. Lapin (1983) has provided a comprehensive review.

Harmaline and related derivatives exert a potent

vasopressin-like effect on sodium and water transport in isolated toad skin, stimulating hydrosmotic flow across the membrane (de Sousa & Grosso 1978; Canessa, Jaimovich & de la Fuente 1973). Failure of harmaline to elicit any effect in preparations pretreated with vasopressin and/or norepinephrine suggested a competitive mechanism of action. Harmine, harmaline and related compounds have tremorogenic effects, cardiovascular effects and also influence homeothermic mechanisms, causing hypothermia in some animals (rats and mice) and hyperthermia in others (rabbits) (Ho 1977).

β-Carbolines also have biological activities other than their effects on neurophysiological systems. For instance, Hopp and colleagues (1976) found that harmine exhibited significant antitrypanosomal activity against *Trypanosoma lewisi*. The mutagenic or comutagenic effect of certain β-carbolines has been noted (Umezawa et al. 1978) and the mechanism responsible may be related to the interaction of β-carbolines with nucleic acids (Remson & Cerutti 1979; Hayashi, Nagao & Sugimura 1977). More recently, the ultraviolet-mediated photocytotoxic and photogenotoxic activity of some β-carboline derivatives has been described (Towers & Abramowsky 1983; McKenna & Towers 1981).

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